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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,775	01/04/2001	David J. Grainger	295.009US3	6351

7590 08/11/2005

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,775	GRAINGER ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *173-194,196-203,205-211 and 231* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *173-194,196-203,205-211 and 231* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

The response filed April 20, 2005 have been received and entered into the application.

The Terminal Disclaimer filed April 20, 2005 has been accepted by the U.S.Patent Office.

Action Summary

The Double Patenting rejection of claims 173-194,196-203, 205-211 and 231 with respect to U.S.Patent No. 5,595,722 is hereby expressly withdrawn in view of Applicant's persuasive argument.

The Double Patenting rejection of claims 173-194,196-203, 205-211 and 231 with respect to U.S.Patent No. 6,117,911 is hereby expressly withdrawn in view of Terminal Disclaimer filed by the Applicants' on April 20, 2005.

Upon further consideration, a new ground(s) of rejection is made as follow:

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 173-194,196-203, 205-211 and 231 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153-173 of copending Application No. 10/729,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending Application teaches an aspect of the claims in the instant application. For example, the method of claim 173 in the present application is similar to the method claimed in claim 153-173 utilizing same biological pathway comprising increasing the level of TGF-beta encompassing utilized same active agents. The copending application teaches the mechanisms of action or biological pathways presently claimed by Applicants and renders obvious the diseased claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 173-194,196-203, 205-211 and 231 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim

8 of U.S. Patent No. 6,410,587B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent disclose and teach an aspect of the claims in the present application. For example the method of claim 173 in the present application is similar to the method claims in 6,410,587B1. The independent claim 173 in instant application is to a method of treating cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering formula (I) encompassed by formula (VI) of the patent. However, the effect is similar as to inhibiting lipid accumulation therefore renders Applicants' claims obvious.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 173-181 and 207-211are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treating a cardiovascular or vascular indication", does not reasonably provide enablement for the "**preventing** a cardiovascular or vascular indication". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a therapeutic method of preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter comprising administering a compound of formula (I) . The nature of the invention is extremely complex in that it encompasses the **actual prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter such that the subject treated with above compounds does not contract lipid accumulation, plaque formulation.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass **prevention** of a complex cardiovascular or vascular indication characterized by a decreased lumen diameter in humans, which has potentially many different causes (i.e. many different mutations or combination of mutations, medical history, hereditary, diet). Each of which may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually **prevent** cardiovascular or vascular indication characterized by a decreased lumen diameter in humans is minimal. All of the guidance provided by the specification is directed towards **treatment rather than prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than **prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans.

State of the Art: While the state of the art is relatively high with regard to treatment of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans. (i.e. atherosclerosis), the state of the art with regard to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in human subjects with the claimed compounds makes practicing the claimed invention unpredictable in

terms of prevention of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to the **prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in human with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding **prevention** of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to **prevent** the

development of a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans in a subject by administration of one of the claimed compounds.

Therefore, a method of **preventing** a cardiovascular or vascular indication characterized by a decreased lumen diameter in humans administering formula I is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 173-181, 205-211 and 231 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 1992).

Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats.

Sawada et al. do not teach a mammal at risk of or afflicted with cardiovascular or vascular indication (atherosclerosis) or mechanism of increasing the level of TGF-beta

to decrease lesion formation or inhibition of lipid accumulation, and dosage formulation and the employment of analogs set forth in claim 176.

It would have been obvious to one of ordinary skill in the art to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis. One would have been motivated to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication such as atherosclerosis because Sawada et al. teach the administration of toremifene citrate (NK622) in 0.1 mg/kg or more including 10mg/kg (cytostatic dose) to female rats showed decrease in total cholesterol in rats. One would be further motivated to make such a modification in order to achieve an expected benefit of lowering total cholesterol level in a mammal suffering from atherosclerosis. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Further, the reference discloses compounds which have a viable utility and are homologs, isomers or close structural analogs of the claimed compounds. The claimed compounds are so closely related structurally to the homologous; isomeric or analogous compounds of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the same properties. That applicant

may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims.

Claims 182-194, 196-203, 205, 206 rejected under 35 U.S.C. 103(a) as being unpatentable over Warri (Dissertation Abstracts International, 1993).

Warri teaches the cellular and molecular mechanism of toremifene involving enhanced mRNA expression of TGF-beta in vitro and in vivo in breast cancer. Warri teaches the growth of breast cancer is inhibited by a new antiestrogen toremifene. (abstract).

Warri does not teach the vivo results involves a mammal suffering diabetes, retinopathy, the effective amounts, and the analogs set forth in claim 202.

It would have been obvious to one of ordinary skill in the art to employ toremifene in a mammal to increase the level of TGF-beta. One would have been motivated to make such a modification because increasing the level of TGf-beta in vivo by toremifene taught by Warri reduces breast cancer. One would have been motivated to increase the level of TGF-beta by employing toremifene in order to achieve an expected benefit of

treating breast cancer in mammal in any population including the patients having any other multiple disorders including diabetes, retinopathy.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sreenivasan Padmanabhan
Supervisory Examiner
Art Unit 1617

Jmk
August 5, 2005